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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2016/2017

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Correlações clínicas da fadiga na esclerose múltipla
Clinical correlates of fatigue in multiple sclerosis

março, 2017

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Clinical correlates of fatigue in multiple sclerosis

Mestrado Integrado em Medicina

Área: Neurologia

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Prof. Doutora Joana Cruz Guimarães Ferreira Almeida

Trabalho organizado de acordo com as normas da revista:

Multiple Sclerosis and Related Disorders

março, 2017

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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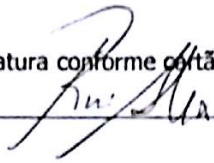

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UNIDADE CURRICULAR PROJETO DE OPÇÃO

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurologia

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Clinical correlates of fatigue in multiple sclerosis

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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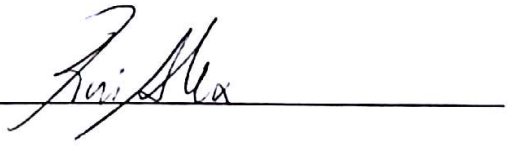
Assinatura conforme cartão de identificação: 

Aos meus pais, pela dedicação, por todas as palavras amigas e todo o auxílio.

Ao meu irmão pela boa disposição e amizade.

À Nicole Pestana Gonçalves pelo amor e apoio incondicional, pela força e encorajamento ao longo destes anos.

Abstract

Background: Fatigue, sleep disorders and neuropsychiatric symptoms are frequently reported in patients affected by Multiple Sclerosis (MS). The relationships between these symptoms are not yet fully understood and their management is difficult in clinical practice. This study was aimed to evaluate the frequency of fatigue, anxiety, depression, vitamin D deficiency and sleep disturbances in patients with MS from our outpatient MS clinic.

Methods: This cross-sectional study sample consisted of 78 adult MS patients. They were analyzed on both their clinical features (type of MS, disease duration, clinical severity, type of treatment, psychiatric medication) and specific scales scores (Expanded Disability Status Scale, Modified Fatigue Impact Scale - MFIS, Hospital Anxiety and Depression Scale- HADS, Epworth Sleepiness Scale - ESS, Sun exposure status scale). Vitamin D levels as measured by 25-hydroxyvitamin D (25-OH-D) serum concentration was obtained.

Results: The prevalence of clinically significant fatigue was 50%; mean MFIS score was 35.72 (SD 19.6), which was significantly higher than in healthy population. There was a strong linear correlation of fatigue with anxiety (r=0.681, p<0.005) and depression (r=0.780, p<0.005). Fatigue was progressively higher with increased clinical disability (p<0.001). Patients reporting insomnia had higher fatigue levels(p<0.023). Low vitamin D levels were seen in 42.6% of patients. Patients with depressive symptoms were more likely to report lower levels of present sun exposure (p<0.037).

Conclusions: Fatigue is a very common symptom in our MS patients, our findings support that higher levels of MS disability are associated with increased fatigue and should be considered. Importantly, we found that fatigue, sleep disturbances and

neuropsychiatric symptoms cluster together and should be recognized and managed in MS patients.

Keywords

Multiple sclerosis; Fatigue; Anxiety; Depression; Sleep disturbances; Vitamin D.

Highlights

- Fatigue is a prevalent symptom in patients with Multiple sclerosis.
- Age, disease duration and clinical disability may impact MS-related fatigue.
- There is a strong link between fatigue, anxiety, depression and poor sleep in MS.
- Hypnotic medication can contribute to fatigue and should be avoided.

1 Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), that results from interactions between susceptibility genes and environmental factors. (Compston and Coles, 2008) The clinical course can be variable, frequently causing several neurological symptoms such as weakness, sensory loss and ataxia but also depression and fatigue. (Compston and Coles, 2008) The first symptoms usually appear between ages 20 and 40 years, effectively representing the most common non-traumatic disabling neurological condition in young adults. (Compston and Coles, 2008)

Fatigue is one of the most prevalent complains in MS, affecting 50 to 74 percent of patients at some point in the disease course. (Hadjimichael et al. , 2008, Putzki et al. , 2008, Weiland et al. , 2015, Wood et al. , 2013) Fatigue is viewed by many patients as one of their most debilitating symptoms. (Krupp et al. , 2010) MS-related fatigue is different from everyday fatigue, as such, occurs in a daily basis, increases during the day

and does not change over time. (Koch et al. , 2008, Krupp, Serafin, 2010, Tellez et al. , 2006, Wood, van der Mei, 2013) Notably, some authors (Runia et al. , 2015) suggest that fatigue can be present in patients with a clinically isolated syndrome (CIS) and increases the risk of developing MS.

Fatigue usually is not associated with demographic factors such as age, gender and disease duration, nor use of immune-modifying therapies. (Hadjimichael, Vollmer, 2008, Krupp, Serafin, 2010, Mills and Young, 2011, Putzki, Katsarava, 2008, Tellez, Rio, 2006) Nonetheless, disease-related factors such as relapse rate, (Tellez, Rio, 2006) mobility impairment (Krupp, Serafin, 2010, Mills and Young, 2011, Tellez, Rio, 2006) and MS subtype (Hadjimichael, Vollmer, 2008, Krupp, Serafin, 2010, Mills and Young, 2011) are associated in some studies with fatigue.

Consequently, MS-related fatigue adversely affects Quality of Life (QoL), (Yamout et al. , 2013) and is linked to early retirement and unemployment. (Hadjimichael, Vollmer, 2008, Krupp, Serafin, 2010, Mills and Young, 2011, Simmons et al. , 2010) While individual studies have provided clinical, demographic and neuroimaging evidence, no single relationship explains fatigue in patients with MS (pwMS) and on-going studies consider it is likely to be multidimensional in its nature. (Krupp, Serafin, 2010) Accordingly, fatigue is usually separated in two categories: primary fatigue thought to be directly involved with MS pathophysiology and secondary fatigue, explained by the consequences of the disease itself, such as sleep disturbances, depression, anxiety, medication, among others. (Krupp, Serafin, 2010, Mills and Young, 2011, Wood, van der Mei, 2013)

Vitamin D insufficiency has been extensively reported in pwMS (Ascherio et al. , 2010, Ascherio et al. , 2014) and has been hypothesised to be an environmental risk factor for MS. (Ascherio, Munger, 2010, Munger et al. , 2006) In fact, some suggest that

vitamin D insufficiency could have a detrimental role not only on MS onset (Ascherio, Munger, 2014, Martinelli et al. , 2014, Munger, Levin, 2006) but also in its clinical course. (Ascherio, Munger, 2014, Fitzgerald et al. , 2015)

Nevertheless, the relationship between MS-related fatigue and vitamin D has received mixed results, while some studies report lower levels of fatigue in vitamin D supplemented pwMS, (Achiron et al. , 2015, Weiland, Jelinek, 2015) others did not found this association. (Ashtari et al. , 2013, Kampman et al. , 2012, Knippenberg et al. , 2014, Runia, Jafari, 2015) The latter could be explained by methodological differences between studies.

Depressive and anxiety symptoms are two variables that theoretically could influence MS-related fatigue. (Learmonth et al. , 2013) The frequency of anxiety and depression among pwMS have been estimated to be higher than the general population (Dahl et al. , 2009) and frequently cluster together with fatigue. (Koch, Uyttenboogaart, 2008, Tellez, Rio, 2006, Wood, van der Mei, 2013)

Sleep disturbances such as restless legs syndrome, chronic insomnia along with others occur more frequently in pwMS. This disorders are associated with excessive daytime sleepiness and can influence fatigue. (Krupp, Serafin, 2010)

MS-related Fatigue is a major but neglected concern in pwMS. Thus, identifying variables that affect fatigue is important and potentially, the investigation of these associations may increase understanding of the pathophysiology mechanisms of fatigue in MS and ultimately help to develop effective treatments.

Therefore, the aim of this study is to investigate the prevalence and severity of fatigue in pwMS and its relationship with other clinical variables.

2 Patients and Methods

2.1 Study participants and design

This was a cross-sectional analysis of adult patients with CIS suggestive of MS and patients with the clinical confirmed diagnosis of MS according with the revised McDonald criteria. (Polman et al. , 2011) followed at the MS clinic of São João Hospital, Porto, Portugal.

Between May 2016 and January 2017, patients who were scheduled to be seen by a physician for routine follow-up were asked to complete a questionnaire and undergo a neurological examination. Patients' medical records were scanned to obtain data on demographics, clinical data, immunomodulatory treatments, use of medication that may confound fatigue assessment (including beta-blockers, beta-interferons, and medication with anti-cholinergic proprieties) or known symptomatic fatigue treatments (eg. Modafinil), antidepressants, antipsychotic and anxiolytic/hypnotic medications and presence of fatigue. Patients with serious cognitive impairment impeditive of answering questionnaires were excluded from the analysis. The Ethic Committee of São João Hospital, Porto, Portugal approved the study protocol and patients gave written informed consent prior to inclusion in the study.

2.2 Study outcome measures

2.2.1 Instruments

Fatigue was assessed using the Portuguese version (Gomes, 2011) of the Modified Fatigue Impact Scale (MFIS). (MSCCPG, 1998) The MFIS consists of a self-administered 21-item questionnaire, validated in Portuguese, that aims to evaluate different features of perceived fatigue. Patients are asked to rate on a 5-point Likert scale how often fatigue influenced them over the past 4 weeks; total score range from 0 to 84, with higher scores indicating severe fatigue. The MFIS was built specifically to assess the impact of fatigue in the daily lives of pwMS and has been extensively used in studies and clinical practice, (Hadjimichael, Vollmer, 2008, Learmonth, Dlugonski, 2013,

Sumowski and Leavitt, 2014, Tellez, Rio, 2006) and has proven to be a reliable and precise instrument. (Learmonth, Dlugonski, 2013) A cut-off value of 38 is the consensus in the literature to distinguish fatigued from non-fatigued pwMS. (Braley and Chervin, 2010)

We also evaluated depressive and anxiety symptoms using the Hospital Anxiety and Depression questionnaire (HADS). The HADS consists of a validated in Portuguese, (Pais-Ribeiro et al. , 2007) self-administered 14-item questionnaire that aims to evaluate different psychological outcomes including 2 scales assessing depression (7 items) and anxiety (7 items) symptoms; sub-scores range from 0 to 21, with higher scores indicating severe depression and anxiety. Clinically significant symptoms are defined at a cut-off value of ≥ 8 for both subscales.

Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS). The ESS consists of a validated in Portuguese, (Sargento et al. , 2015) self-administered 8-item questionnaire, that aims to evaluate sleepiness or the propensity to fall asleep in everyday life situations. Patients are asked to rate on a 4-point Likert scale how often they doze in different settings; total score range from 0 to 24, with higher scores indicating greater propensity to fall asleep. Excessive daytime sleepiness is defined at a cut-off value of 11. Other relevant data included self-reported sleep habits.

2.2.2 Vitamin D

Vit D3 obtained from production in the skin and diet is metabolized into 25-hydroxyvitamin D (25-OH-D) in the liver. The latter serum concentration has been used in the majority of studies to screen vitamin D status. (Ascherio, Munger, 2010, Holick, 2007)

Most patients provided a blood sample and serum concentration of 25-OH-D was measured; a cut-off value of ≤ 50 nmol/L and a cut-off value of ≤ 72 nmol/L were used

to categorize patients with vitamin D deficiency and relative insufficiency respectively. (Holick, 2007)

Measurement of past sun exposure through recall by adults has been shown to be a valid and reliable way of assessing indirectly Vitamin D status. (van der Mei et al. , 2006) Sun Exposure status was calculated using a recall questionnaire (Hanwell et al. , 2010) assessing daily time in sun and skin exposure (face, limbs, body) for the previous week; score ranges from 0 to 56 with higher scores indicating more time per week outdoors and with more skin exposed to the sun.

2.3 Clinical data

Annualised relapse rate (Ascherio, Munger, 2014, Fitzgerald, Munger, 2015) was assessed through patients' reported relapses at study visit and retrospectively, IV methylprednisolone treated relapses were checked using patients' medical records.

To evaluate neurological impairment we used the Expanded Disability Status Scale (EDSS), a well-established method to quantify disability in MS. (Kurtzke, 1983)

2.4 Statistical analysis

Continuous variables were summarised using mean and standard deviation (SD) and categorical variables using number and percentage. The univariate relationships between continuous variables were assessed using Student *t* test and categorical variables were compared using the χ^2 test. Correlation analysis with Pearson product-moment correlation coefficient (r) was used to assess the association of two continuous variables. Strength of the relationship between variables was considered small (r=0.10 to 0.29), medium (r=0.30 to 0.49) and large (r=0.50 to 1.0). A p value of ≤ 0.05 was considered statistically significant. IBM SPSS Statistics 23 (IBM corp., New York, USA) was used for the analysis.

3 Results

3.1 Participants

Seventy-eight patients (51 women and 27 men) fulfilled the inclusion criteria and were included in the study. Mean age of the study sample was 38 (range 18-65 years). The mean disease duration was 7.0 years (range 0-23 years) with mean age at diagnosis 30.4 (SD 10.7); mean EDSS was 1.6 (SD 1.5). Disease course was as follows: 55% participants with relapsing-remitting MS, 25% with secondary progressive MS and 20% with CIS. Participants characteristics according to fatigue levels are presented in Table 1.

Table 1: Demographic, Clinical characteristics and treatment plans by fatigue severity.

	Fatigue (n=33)	No fatigue (n=32)	*p* value
Demographics			
Mean age, years (sd)*	41 (10.7)	32 (9.9)	<0.001
Gender, n (%)**			n.s.
Male	10 (45.5)	12 (54.5)	
Female	23 (30.3)	20 (37.5)	
Clinical characteristics			
Disease duration, mean (sd) (months)*	102 (84)	60 (56)	< 0.021
Age at diagnosis, mean (sd) (years)*	32.06 (9.89)	26.77 (9.87)	<0.038
MS subtype, n (%)**			n.s.
Relapsing remitting	16 (26.7)	15 (25)	
Primary or secondary progressive	10 (16.7)	5 (8.3)	
CIS	6 (10)	8 (13.3)	
EDSS, mean (sd)*	1.96 (1.69)	1.05 (0.97)	<0.015
Treatment, n (%)			
Immunomodulatory**	18 (28.6)	20 (31.7)	n.s
Interferon beta	11 (17.2)	16 (25)	
Glatiramer acetate	2 (3.1)	3 (4.7)	
Dimethyl fumarate	5 (7.8)	2 (3.1)	
Immunosuppressive**	9 (14.4)	10 (15.9)	n.s
Natalizumab	5 (7.8)	6 (9.4)	
Fingolimod	4 (6.3)	4 (6.3)	
No treatment**	5 (7.9)	1 (1.6)	n.s

EDSS, Expanded Disability Status Scale; *t test ** χ^2; n.s, non-significant (p>0.05)

Patients reporting fatigue were likely to be older. Blood samples for vitamin D measurements were available for 54 patients. The non-responders did not differ in mean age, gender distribution, disease duration from responders (data not shown).

3.2 Fatigue

Thirty-three patients (50%) suffered from fatigue, and the mean MFIS score for patients was 35.72 (SD 19.6). In healthy individuals from the literature(Gomes, 2011), the mean MFIS was 23 (SD 12.24) which was significantly lower than in our patients

(p<0.0005). MFIS scores were not associated with gender. As shown in Table 1, fatigued patients were likely to be diagnosed at an older age, had longer disease duration, and more disability as reflected in the EDSS at inclusion consultation than non-fatigued patients. The prevalence and severity of fatigue was similar in patients with relapsing-remitting, secondary progressive and primary progressive MS. Fatigue levels did not differ between CIS patients and clinically definitive MS patients.

3.3 Vitamin D

The mean serum 25-OH-D concentration of patients was 31.53 ng/mL (SD 19.61). Twenty-three patients (42.6%) had low vitamin D levels (<29ng/mL) and 15 patients (27.8%) had vitamin D deficiency (<20ng/mL). The mean 25-OH-D concentration among those with fatigue was 29.5 ng/mL (SD 13.3) and 35.0 ng/mL (SD 26.2) among non-fatigued patients as shown in table 2.

Table 2: Scales scores, laboratory values and annualized relapse rate by fatigue severity.

	Fatigue (n=33)	No fatigue (n=32)	p value
Scales			
HADS A, mean (sd)*	11 (3.9)	4.7 (2.6)	<0.0005
HADS D, mean (sd)*	9 (2.8)	2.7 (2.5)	<0.0005
ESS, mean (sd)*	3.2 (3.40)	2.5 (2.86)	n.s
Psychiatric medication, n (%)			
Antidepressant**	14 (22.2)	5 (7.9)	<0.035
Antipsychotic	7 (11.1)	0	
anxiolytic/hypnotic**	9 (14.3)	3 (9.7)	n.s
Sun exposure score, mean (sd)*	16.6 (5.35)	18.4 (4.5)	n.s
Laboratory values			
25-OH-D, mean (sd), (ng/mL)*	29.5 (13.3)	35.0 (26.2)	n.s
Disease activity			
Annualized relapse rate, n (%)*	10 (30.3)	7 (18.7)	n.s

HADS A and D, Hospital Anxiety and Depression Scale; ESS, Epworth Sleepiness Scale; 25-OH-D, 25-hydroxyvitamin D; *t test ** χ^2; n.s, non-significant (p>0.05)

We found no association between 25-OH-D levels and presence of fatigue, anxiety or depression. Twenty-seven patients (34.6%) were taking vitamin D-containing supplement.

3.4 Neuropsychiatric symptoms

Fifty-nine patients (75.6%) reported clinically significant neuropsychiatric symptoms: anxiety was reported by 39.7% of patients and depressive symptoms were present in 35.9%. There were no significant differences between gender. MFIS strongly correlated with both anxiety (r=0.681, p<0.005) and depression (r=0.780, p<0.005). (see table 2). Fatigue levels were significantly higher in patients using antidepressants, antipsychotic and anxiolytic/hypnotic medications 46.0 (SD 15.9) vs 28.9 (SD 19.04) (p<0.0005). Patients with clinically significant depressive symptoms were significantly more fatigued 49.7 (SD 13.0) vs 24.72 (SD 16.8) (p<0.0005).

3.5 Treatment

Forty-six patients (59%) were treated with immunomodulatory agents: 37.2% were on treatment with one of the INF-β preparations, GLA 10.3%, Dimethyl fumarate (DMF) 10.3% or Teriflunamide 2,6%. Thirty-nine patients (50%) were treated with immunosuppressive agents: the most frequently used was Natalizumab 15.4% followed by Fingolimod 10.3%. Eleven patients (14.1%) were given Fampiridine and 5 patients were not under disease modifying treatment. Fatigue levels were not associated with any of the treatments plans, nor between treated and untreated patients (see table 2). Two patients (2.6%) were receiving pharmacological treatment for fatigue, namely modafinil.

3.6 Sleep

The mean total sleep time was approximately 10h (SD 3h), total sleep time did not differ between fatigued and non-fatigued patients and 43.6% of patients reported insomnia. Fatigue levels differ significantly between patients reporting insomnia 41.4 (SD 18.2) vs 27.5 (SD 21.8) (p<0.023), similarly patients reporting insomnia had significantly more anxiety symptoms 9.5 (SD 4.5) vs 6.2 (SD 4.5) (p<0.018). There was no association between sleeping during the day and fatigue levels (see table 2). The

prevalence of excessive daytime sleepiness was 3.8% and there was no correlation between fatigue and sleepiness as assessed by the ESS scores.

3.7 Sun exposure

There was no correlation between sun exposure indicators (vitamin D and Sun exposure score). Present sun exposure (hours) was not a predictor of vitamin D level or MFIS score. Patients with depressive symptoms were more likely to report lower levels of present sun exposure ($p<0.037$).

3.8 Relapses

In the year prior to the study, 10 relapses occurred in 30.3% of fatigued patients and 7 relapses involved 18.7% of non-fatigued patients (see table 2). Fatigue levels were not associated with annualized relapse rate.

4 Discussion

Although often discussed in recent years, the pathophysiology of fatigue in MS remains unclear. (Braley and Chervin, 2010, Induruwa et al. , 2012) Until today, no single relationship explains fatigue in pwMS and on-going studies consider it is likely to be multidimensional in its nature. Accordingly, fatigue is usually separated in two categories: primary or central fatigue thought to be directly involved with the pathogenic mechanisms of MS including immunological factors and central nervous system damage, such as pro-inflammatory cytokines, lesion load, compensatory brain reorganization, axonal injury and hormonal influences. (Braley and Chervin, 2010, Induruwa, Constantinescu, 2012) And secondary fatigue, explained by the consequences of the disease itself, such as sleep disorders, depression, anxiety, iatrogenicity, nociceptive pain among others. (Braley and Chervin, 2010, Krupp, Serafin, 2010)

This cross-sectional study aimed to determine fatigue prevalence in pwMS and its relation with several clinical variables using validated questionnaires and objective clinical assessment. Our study adds to the current knowledge about fatigue in pwMS since few previous studies have reported secondary conditions that contribute to fatigue.

The prevalence of clinically significant fatigue, depression and anxiety was 50%, 35.9% and 39.7% respectively. 43.6% of patients reported sleep problems.

The high prevalence of clinically significant fatigue (50%) reported here is consistent with previous studies that shown similar results (Hadjimichael, Vollmer, 2008, Putzki, Katsarava, 2008, Weiland, Jelinek, 2015, Wood, van der Mei, 2013) and demonstrates that MS-related fatigue impacts activities of daily living as assessed by the MFIS. Our assessment of fatigue levels revealed that patients differed on several disease characteristics: fatigued patients were older, had a longer disease course and suffered from greater clinical disability. Notably, fatigued patients were likely to be diagnosed at an older age. Furthermore, as previously described, (Mills and Young, 2011, Putzki, Katsarava, 2008) we did not find differences in gender for fatigue levels.

Such findings are consistent with large investigations that linked older age and disease duration (Hadjimichael, Vollmer, 2008) with increased fatigue levels in pwMS. We found that fatigued patients also had increased disability levels as assessed by the EDSS, which is in line with previous studies that found a clear increase in fatigue with higher mobility impairment (Hadjimichael, Vollmer, 2008) and MS impact. (Mills and Young, 2011) It is important that clinicians recognize fatigue in pwMS even in those with reduced ambulation.

In our study, fatigue occurred among patients of all MS subtypes including CIS patients and there was no significant association in MS subtype with the level of fatigue.

We agree with previous studies that found that MS-related fatigue occurs independently of the type of MS and can be present at the time of CIS. (Runia, Jafari, 2015)

There have been only a few studies evaluating the effect of immune-modifying therapies and fatigue. We compared treatment modalities and found no difference between individuals on different immune-modifying therapies. Additionally, we found no relationship between fatigue levels in treated versus untreated patients. These findings are in keeping with previous studies. (Hadjimichael, Vollmer, 2008, Putzki, Katsarava, 2008)

Our assessment revealed no important influence of continuous 25-OH-D serum levels nor recently reported sun exposure on fatigue levels. Patients who had Vitamin D deficiency (<20ng/mL) were no more fatigued than vitamin D sufficient patients. Although vitamin D deficiency has strongly been linked to MS risk (Martinelli, Dalla Costa, 2014, Munger, Levin, 2006) progression and activity, (Ascherio, Munger, 2010) the evidence for the influence of vitamin D serum levels on MS-related fatigue is sparse. A longitudinal study (Knippenberg, Damoiseaux, 2014) found no relationship between vitamin D levels and MS-related fatigue, interestingly, they did however, found that higher self-reported sun exposure was related to lower levels of fatigue.

In the present study, patients with depressive symptoms were more likely to report lower levels of present sun exposure. It is conceivable that pwMS experiencing more depression symptoms could refrain from outdoor activities and this could account for the apparent relationship between sun exposure and fatigue. A randomized controlled trial (Achiron, Givon, 2015) found that vitamin D supplementation decreased fatigue levels on severely fatigued pwMS. We did not found such association as vitamin D supplemented patients experienced similar fatigue levels vs non-supplemented patients.

The prevalence of neuropsychiatric symptoms reported here is similar to that previously reported in MS (Dahl, Stordal, 2009, Knippenberg, Damoiseaux, 2014, Wood, van der Mei, 2013) and considerably higher than was reported in non-MS population. (Dahl, Stordal, 2009) In a population-based study, (Dahl, Stordal, 2009) a significant proportion of pwMS reported anxiety (30.2%) and depressive symptoms (25.7%). Previously there have been conflicting results between the relationship of anxiety and depressive symptoms with fatigue in pwMS, while it has been proven that the overlap of these symptoms are higher than the expected, (Wood, van der Mei, 2013) some studies found a weak correlation between these symptoms, (Mills and Young, 2011) with the association largely confined to woman. (Dahl, Stordal, 2009) A longitudinal study (Koch, Uyttenboogaart, 2008) found that fatigue and depressive symptoms occurred together in 40% of pwMS and prevailed at the same intensity for 10 years of follow-up. The disagreement in the literature may be due to variability in defining and measuring fatigue levels or differences in patients' population.

In the present study, we found a strong linear correlation between fatigue and both anxiety and depressive symptoms. The concurrence of fatigue and neuropsychiatric symptoms was expected since not only is depression itself associated with similar symptoms (loss of motivation, anhedonia), (Braley and Chervin, 2010, Krupp, Serafin, 2010) but this association could occur due to similar pathogenic mechanisms and may involve gray matter atrophy of specific brain regions (Gobbi et al. , 2014, Nygaard et al. , 2015) making this intimate relationship even more complex. Similarly, in this study, patients receiving psychiatric medication were likely to be more fatigued. This apparent association could be explained by the overlap of fatigue and depressive symptoms and therefore, more likely to be selected for these treatments. However, this could also entail that regardless of any contributory part of depressive symptoms to fatigue, psychiatric

medication was not particularly effective in fatigue. Aside from the contributing part of neuropsychiatric symptoms to fatigue, these symptoms are associated with substantial suicidal risk (Jose Sa, 2008) and therefore, the presence of fatigue should raise clinical awareness for these symptoms and thereby promote their evaluation and treatment.

We found that fatigue levels and anxiety symptoms were higher in patients reporting insomnia, these findings are in keeping with the literature where it seems that disrupted nocturnal sleep may contribute to fatigue in MS. (Mills and Young, 2011) Sleep disturbances are more common in pwMS than the general population (Braley and Chervin, 2010, Brass et al. , 2014, Krupp, Serafin, 2010) and the rate of chronic insomnia is reported to be 31.6% by the largest study to date. (Brass, Li, 2014) Not only are specific conditions such as central sleep apnea, restless legs syndrome, narcolepsy more frequently present in pwMS (Braley and Chervin, 2010, Brass, Li, 2014) which are often associated with fatigue, but also poor sleep may arise from MS-related symptoms, (Krupp, Serafin, 2010) these include neuropsychiatric symptoms, spasticity, nocturia and iatrogenicity. (Braley and Chervin, 2010, Brass, Li, 2014, Krupp, Serafin, 2010) The association between sleep disturbances and fatigue is still in debate, a recent study (Mills and Young, 2011) demonstrated a link between sleep and MS-related fatigue, suggesting a "V" shape relationship between duration of nocturnal sleep and fatigue, being 7.5h of total sleep time associated with the lowest levels of fatigue and both lower and higher sleep times being deleterious. They also found a weak correlation between sleepiness as assessed by the ESS and fatigue. Severe fatigue levels in pwMS should prompt the physician for the possibility of underlying sleep disturbances which should be addressed and treated. In this matter, in the present study, patients receiving hypnotic medication, which is frequently used to improve nocturnal sleep, was actually detrimental to fatigue. This apparent contradiction can be explained by the difficulty to differentiate between

fatigue and daytime somnolence (Braley and Chervin, 2010) that could be being reported, and carryover effects from hypnotic use could be influencing fatigue levels, and for this reason, physicians should promote alternative treatments for insomnia in pwMS. (Braley et al. , 2015)

The strength of our study is that patients were examined at our outpatient department which enabled us to obtain a clinical assessment of fatigue related variables. A limitation of our study is its cross-sectional design. Since data were not collected prospectively, a longitudinal evaluation of fatigue is not possible and it is possible that our findings could be attributed to reverse causality. Nevertheless, our findings are in agreement with previous studies.

5 Conclusions

In conclusion, half of pwMS in our sample reported severe fatigue that impacts patients' daily lives. Presence of fatigue and its severity were associated with age, disease duration and clinical disability and seems to be relatively independent of MS subtype and treatment modality. We suggest that poor sleep, anxiety and depressive symptoms and psychiatric medication are significantly associated with fatigue in pwMS. Neuropsychiatric symptoms overlapped with fatigue. These findings suggest that non-central causes could have a substantial contribution to MS-related fatigue and should be actively investigated and treated.

6 Acknowledgements

The authors would like to thank Dr. Mafalda Seabra for her assistance in survey administration and Dr. Nicole Pestana for her assistance in data management.

7 Declaration of conflicting interests

The Authors declares that they have no conflict of interest.

8 Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Agradecimentos

À Professora Doutora Joana Guimarães, minha orientadora, estou profundamente grato por ter aceitado o risco de me guiar nesta dissertação e pela forma como me apoiou e aconselhou. Foi pela sua "mão" que conheci o mundo da Neurologia e em particular as doenças desmielinizantes. Permitiu-me uma liberdade de pensamento e uma autonomia, que muito agradeço. Obrigado.

À Dra. Cláudia Sousa cujo trabalho desenvolvido contribuiu para a presente dissertação agradeço a sua colaboração.

À Dra. Mafalda Seabra por toda a ajuda no processo de colheita de dados.

Por fim, agradeço a todos os doentes que aceitaram participar nesta investigação.

MULTIPLE SCLEROSIS AND RELATED DISORDERS

AUTHOR INFORMATION PACK

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Material and methods
Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

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• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
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A structured abstract that includes the headings: Background, Methods, Results, and Conclusion is required. The abstract must not exceed 500 words. **Background.** The background should provide a brief and concise description of the background and reason for the study citing relevant literature overview, and a clear statement of hypothesis, and study objectives. The introduction should not be an exhaustive review of the literature. **Methods.** This section provides a concise description of the procedural, experimental, and statistical methods in sufficient detail to allow other investigators to reproduce the study. **Results.** State concisely the results of the study. **Conclusion.** Briefly summarize the major conclusions of the investigation.

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Acknowledgements
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List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

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If no funding has been provided for the research, please include the following sentence:

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Citations may be made directly (or parenthetically). Groups of references should be listed first alphabetically, then chronologically.
Examples: 'as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999). Kramer et al. (2010) have recently shown ....'
List: References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication.
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Van der Geer, J., Hanraads, J.A.J., Lupton, R.A., 2010. The art of writing a scientific article. J. Sci. Commun. 163, 51–59.
Reference to a book:
Strunk Jr., W., White, E.B., 2000. The Elements of Style, fourth ed. Longman, New York.
Reference to a chapter in an edited book:
Mettam, G.R., Adams, L.B., 2009. How to prepare an electronic version of your article, in: Jones, B.S., Smith , R.Z. (Eds.), Introduction to the Electronic Age. E-Publishing Inc., New York, pp. 281–304.

Reference to a website:
Cancer Research UK, 1975. Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/ (accessed 13.03.03).
Reference to a dataset:
[dataset] Oguro, M., Imahiro, S., Saito, S., Nakashizuka, T., 2015. Mortality data for Japanese oak wilt disease and surrounding forest compositions. Mendeley Data, v1. http://dx.doi.org/10.17632/xwj98nb39r.1.

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The author is responsible for obtaining all necessary consents from patients for (i) the performance of any medical procedure involved, as well as (ii) a release permitting our use of the relevant material. It is our insurers' preference that we do not have any direct contractual relationship with the patients themselves. Please download the Patient consent form here

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274-16

Unidade de Investigação

Tomei conhecimento. Nada a opor.

09 de Janeiro de 2017

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

AUTORIZADO

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Presidente do Conselho de Administração

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DIRECÇÃO CLÍNICA

Aprovado. Ao CA. 27/1/2017

(Prof.ª Doutora Ana Azevedo)

Exmo. Senhor
Presidente da Comissão de Ética para a Saúde do Centro Hospitalar de S. João/Faculdade de Medicina da Universidade do Porto

Assunto: Pedido de apreciação e parecer para estudo/projecto de investigação

Nome do Investigador Principal: Rui Alexandre Cró Freitas

Título do projecto de investigação: Clinical correlates of fatigue in multiple sclerosis

Pretendendo realizar no(s) Serviço(s) de Neurologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, a sua apreciação e a elaboração do respectivo parecer.
Para o efeito, anexo toda a documentação referida no dossier dessa Comissão respeitante a estudos/projectos de investigação.

Com os melhores cumprimentos.

Porto, 30 / Dezembro / 2016

O INVESTIGADOR/PROMOTOR

Comissão de Ética para a Saúde do HSJ
Parecer

Projeto de investigação: "Clinical correlates of fatigue in multiple sclerosis".

Promotor:

- Não aplicável.

Concepção e pertinência do estudo

- Trata-se de um estudo a realizar no âmbito da tese de Mestrado Integrado em Medicina na Faculdade de Medicina da Universidade do Porto (FMUP), que tem como objetivo, avaliar do ponto de vista clínico doentes com Esclerose Múltipla seguidos no Serviço de Neurologia do Centro Hospitalar de S. João (CHSJ), nomeadamente, a relação existente entre a fadiga e: a) características psicológicas (ansiedade e depressão), comportamentais (exposição solar), perturbações do sono, terapêutica imunomoduladora e variáveis de progressão de doença (EDSS, subtipo de Esclerose Múltipla, Recaídas); b) níveis séricos de vitamina D.
- Serão colhidos dados sócio-demográficos (incluindo a raça e a etnia), dados sobre a duração e gravidade da doença, ano do diagnóstico, evolução, tratamentos e recidivas, uso de medicação que pode explicar a fadiga, e a presença da fadiga.
- Os critérios de inclusão e exclusão e o exame neurológico serão efectuados por um Neurologista.
- Serão usados os seguintes instrumentos: formulário do tratamento e da modalidade farmacológica; questionários validados para a população portuguesa da depressão e ansiedade (HADS) e da fadiga (MFIS); escala da exposição ao sol; questionário das perturbações do sono (ESS).
- A concentração plasmática da vitamina D será avaliada na primeira consulta ("baseline") e aos 6 meses.
- *A este propósito, no protocolo submetido à CES, não é explícito se os questionários/instrumentos mencionados, serão efectuados apenas uma vez ou se serão repetidos aos 6 meses (como a quantificação da vitamina D) e em ambiente de consulta programada (para evitar deslocações e despesas adicionais).*
- O estudo terminará em março de 2017 e não terá nem precisará de qualquer apoio financeiro (procedimentos habituais no seguimento dos doentes com a patologia em estudo).

- O estudo é importante, pertinente e está muito bem fundamentado.
- O protocolo do estudo, os critérios de inclusão e exclusão estão suficientemente detalhados e não colocam objeções do foro ético.
- *No protocolo submetido à CES consta como Investigador Principal, Rui Alexandre Cró Freitas, estudante do 6º ano do curso de Medicina da FMUP, tendo como elo de ligação (e orientador da Tese) a Médica especialista de Neurologia do Hospital de S. João EPE e Professora da FMUP, a Professora Joana Guimarães). Dado haver vários procedimentos médicos contemplados no estudo, a Investigadora Principal deve ser a Professora Joana Guimarães, que obviamente dispõe das competências técnicas e científicas para a realização do estudo.*
- O estudo será realizado no Serviço de Neurologia do Centro Hospitalar de S. João EPE que dispõem das condições necessárias para a realização do estudo, e está autorizado pelo Diretora de Serviço, a Professora Carolina Garrett.

– **Beneficio/Risco**

- Dada a natureza do estudo não haverá riscos ou incómodos significativos (serão efetuados todos os procedimentos clínicos, imagiológicos e analíticos habituais à patologia em estudo). Os conteúdos dos questionários são pertinentes e adequados aos objectivos do estudo.
- Poderá haver algum benefício relacionado com a possível identificação dos factores que explicam a fadiga e potencial aplicação de terapêutica mais adequada.

Respeito pela liberdade e autonomia do sujeito do ensaio

- A folha de informação submetida à CES contém a informação relevante relacionada com o tipo de estudo proposto.
- Estão consignados os direitos e referenciadas as (não) consequências para o sujeito do estudo em não participar e, uma vez dado o seu consentimento, ter a possibilidade de exercer o direito de não continuar no estudo sem que daí resulte qualquer modificação dos cuidados médicos a prestar.

– **Confidencialidade dos dados**

A confidencialidade dos dados está garantida.

– **Indemnização por danos**

Não aplicável.

– **Continuação do tratamento**

Não aplicável.

- **Propriedade dos dados**

Não aplicável.

Conclusão

Em face da análise do protocolo do estudo "Clinical correlates of fatigue in multiple sclerosis", proponho a sua aprovação pela CES do HSJ/FMUP, depois de obtida as respostas às questões formuladas em sublinhado e em itálico.

Porto, 18 de outubro de 2016

O Relator
Prof. Manuel Vaz Silva

RESPOSTAS ADEQUADAS ÀS QUESTÕES FORMULADAS.

30/11/2016

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☒
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Joana Cruz Guimarães Ferreira Almeida, abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 17 / 10 / 2016.

O Investigador Principal

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

18/10/16

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO/FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

emitido na reunião plenária da CES de ___/___/___

Centro Hospitalar **São João**

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

30/11/16